Amendments to the Drawings

The attached sheets of drawings includes revised Figures 4.2 and 6.2 objected to because a portion of the text was allegedly unreadable. Replacement drawing sheets are hereby provided having readable text. No new matter is added by way of the replacement drawings.

REMARKS AND ARGUMENTS

Status of claims:

In a previous paper claims 24-41 were withdrawn and claim 12 was cancelled. In the present paper, claims 1, 3, 6, 9, 13, 14 and 18 are amended. No new matter is added by way of these amendments and the claim language is fully supported by the application, as filed.

Examiner Interview

On September 12, 2006, attorneys Leeck and Fairman, Agent/Owner Heisler and applicant Abbott conducted a telephonic interview with Examiners Foster and Le. The various rejections were discussed, in particular, the grounds for those rejections based on the combination of U.S. Patent 6,852,285 and Bernard et al. The present amendments and arguments are based on that discussion.

Sequence compliance

In the Office Action mailed July 12, 2006, the Specification was objected to because the identifier "Artificial" in the numeric identifier <213> did not further include the identifier "Synthetic" for SEQ ID NO: 2. A replacement sequence listing has accordingly been filed electronically with the Office fulfilling these requirements on September 11, 2006. The recently-filed sequence listing shall replace the prior version. Entry of the replacement sequence listing into the application is requested.

Drawings

In the Office Action mailed July 12, 2006, an Objection to Figures 4.2 and 6.2 was maintained because portions of the text were still found to be unreadable and the replacement sheets did not include all the figures. Accordingly, replacement figures are now provided for

enhancing clarity of the original drawings. Entry of the replacement drawings into the application is hereby requested. The replacement drawings are appended at the end of this response. No new matter has been introduced in the replacement drawings.

Claim objections

Claim 14 is objected to because it depended from claim 12. Claim 14 has now been amended to depend from claim 1. Claim 23 was objected to because the Office found it unclear how the detecting the orientation of the liquid crystal related to the detection of the ligand in claim 1. However, claim 1 has now been amended to recite that changes in the liquid crystal orientation indicate the presence of the ligand. Thus, claim 23 now provides a clear recitation of the claimed invention. In view of these amendments applicants believe that the objections to claims 14 and 23 have now been overcome.

REJECTIONS TO THE CLAIMS

1. Claim rejections under 35 U.S.C 112, first paragraph

In the Action, claim 13 was rejected as failing to comply with the written description requirement. Specifically, the Office states that as amended in the previous Office Action, claim 13 recited that "each receptor" "independently has specificity for one ligand" and that the liquid crystal is capable of detecting the presence of "more than one ligand." The Office states that it is unclear what is meant by each receptor "independently having specificity." The Office continues "the claim encompasses a scenario in which multiple different receptors all having specificity for the same ligand are used, which represents a departure from the specification and claims as originally filed". Further, the Office continues, "[A]pplicant points to the specification at [0181], in which different antibodies were arrayed in order to detect phosphorylated proteins. There is no specific disclosure in this section that the different antibodies "independently have specificity

for the same ligand. Furthermore, applicant has not established that the specific antibodies referred to are necessarily and always specific for the same one ligand, and that such a feature would have been recognized as such by those skilled in the art."

In fact, the Examiner's characterization is correct. The passage referred to at [0181] states that "the following antibodies could be arrayed: pan-reactive 111.6 Ab (Lab Vision), and phosphor-specific antibodies anti-pY1068 (Biosource), anti-pY1086 (Biosource), anti-pY1148 (Biosource), and anti-pY1173 (Upstate)." As stated in the specification, all the above recited antibodies are specific to epidermal growth factor (the "ligand" in this case). Further, as described in the accompanying Product Analysis sheets (provided for the Examiner's convenience as Appendix I) and as is understood by those of skill in the art, using the nomenclature of antibodies, pY refers to a tyrosine ('Y') which is phosporylated (lower case 'p') at a particular residue (either 1068, 1086 or 1148 in the above case). Further, the pan-reactive 111.6 is immunogenic to the extracellular domain. Thus, contrary to the Office's assertion that a scenario is encompassed that this represents a departure from the specification because multiple, different receptors all having specificity for the same ligand are encompassed, is untrue. The specification, explicitly recites antibodies which all have different specificities for the same ligand (EGFR in this case) and further all the recited antibodies have different immunogenicity. In addition, for those of skill in the art, at the time the invention was made it was well recognized that one of the uses for the antibodies is to identify whether the specific residues to which the antibody was raised, are phosphorylated or not. Thus, the specification explicitly teaches a scenario in which each receptor independently has a specificity for one ligand. Accordingly, this part of the rejection is overcome and should be withdrawn.

The Office also states that the "Applicant has not established that the specific antibodies referred to are necessarily and always specific for the same one ligand and that such a feature

would have been recognized by those skilled in the art." In fact, as evidenced by the appended Product Data sheets (Appendix I) this is in fact the case. It was well recognized long before the invention was made that antibodies bind specifically to a particular epitope. This understanding is well documented in any immunology textbook and is one reason that antibodies find such well-spread use, not only in research but also therapeutically because their specificities to not change. This feature is further documented in the product data sheets included in Appendix I. Thus, this part of the rejection is overcome and should be withdrawn.

Further, the Office states that "the specification does not provide any generic teaching of a method wherein each of a plurality of receptors "independently" have a specificity for one ligand, or of a method, recited in [Para 181] with different receptors all having specificity for the same one ligand." This statement is also a mischaracterization of the disclosure. In fact, the specification does disclose a method wherein a plurality of receptors (111.6, pY1068, pY1086, pY1148 and pY1173) all having specificities to different epitopes of the same ligand are layered on the same array. Thus, this part of the rejection is overcome and should be withdrawn.

The Office continues, "the reliance on a single or limited species (the specific antibodies of [0181] . . . does not provide sufficient direction and guidance to the features currently claimed. This specific example pointed by applicant relates to a particular set of reagents, while claim 13 is not limited in scope to such reagents. The disclosure of a single species in which multiple different receptors may have specificity for the same ligand fails to support the genus that is now claimed. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads." This characterization is further unfounded. First, it should be pointed out that the antibodies described have specificities for different epitopes of the same ligand. Thus, each antibody is capable of binding its ligand independently of the other antibody. Therefore, they cannot be considered a single species as each antibody is separately constructed

and recognizes a different epitope. For example, pY 1068, pY1086 and pY1148 only recognize those particular tyrosine residues when they are phosphorylated. Thus, the antibodies can be considered to recognize separate ligands were the ligand of interest the unphosphorylated EGFR. Accordingly, not only are the antibodies specific to the particular residues they are specific to the residues phosphorylation state. Because the antibodies described in [0181] have different provenances, different recognition sites and (with the exception of 111.6) are phospho-specific, they constitute multiple species by which to support the claimed genus. Further, because pY1068, pY1086 and pY 1148 are specific only to those particular residues that are phosphorylated, e.g., different ligands. Thus, multiple receptors and multiple ligands are herein described which fully support the scope of the invention as claimed. Thus, this part of the rejection is overcome and should be withdrawn.

2. Claim rejections under 35 U.S.C 112, second paragraph

Claims 1-11 and 13-23 are rejected under 35 U.S.C. 112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject which Applicants regard as the invention.

Specifically, claim 1 is rejected because it recites the limitation in lines 6 and 8 "the receptor" while line 2 refers to a "plurality of receptors". As amended herein, claim 1 now recites "a receptor" including two or more receptors of different specificity . . .." Specific support for this amendment is found in the specification at, for example paragraph 181 describing the use of multiple receptors having different specificities, each receptor being 'a' receptor. Thus, this aspect of the rejection is overcome and should be withdrawn.

Claim 1 is further rejected because the claim recites the limitation, in part (c), "the detection surface having a detection substrate and a liquid crystal" has insufficient antecedent

basis in view of the recitation "detection surface" in part (b). This rejection is overcome by the amendment to the claim which now recites, "detecting the presence of the ligand on the detection surface using a detection substrate having a liquid crystal, wherein the presence of the ligand is detected by a change in the orientation of the liquid crystal." Specific support for this amendment is found in the specification, at for, example, paragraphs 37, 38, 154, 155, 162, 163, 183 and illustrated in, at least, Figures 4 and 4.1. Thus this aspect of the rejection is overcome and should be with drawn.

Claim 1 is further rejected as being indefinite for the recitation "having a detecting substrate and a liquid crystal" in part (c). As now amended (see above), the claim now recites that the liquid crystal is in contact with the detection substrate and not the affinity substrate as was, apparently, understood by the Office previously. Thus, this aspect of the rejection is overcome and should be with drawn. Specific support for this amendment is found in the specification at, for example, [Para 24]-[Para 27] and [Para 90]-[Para 107]. No new matter has been added by way of this amendment.

Claim 3 is rejected because the claim recites a Markush group that is terminated with the phrase "or a fragment thereof." The claim has now been amended to omit the phrase, "or a fragment thereof." Thus, the rejection has been overcome and should be withdrawn. No new matter has been added by way of this amendment.

Claim 6 is rejected because it recites a method wherein PDMS is "peptide-terminated" and it is unclear what is meant by "peptide-terminated". As amended herein the claim now recites that "PDMS is further ~~peptide~~-terminated by a peptide moiety." Specific support for this amendment is found in the specification at, for example, Example 11 spanning paragraphs 193 to 196 describing the conjugation of peptide molecules to the treated PDMS stamps. No new

matter has been added by way of this amendment. Thus, the rejection has been overcome and should be withdrawn.

Claims 7 and 9 are rejected for reciting a method wherein a species is "capable of binding to" a phosphorylated peptide (claim 7) or protein (claim 9). The Office finds the claims indefinite because it would appear that the bound species would correspond to the ligands recited in claim 1. Claim 7 has now been amended to recite that the PDMS is capable of binding to a phosphorylated ligand. Specific support for this amendment is found is the specification at, for example, paragraph [0181] where the binding of the receptor terminated PDMS is specific for various phosphorylated epitopes (see above). No new matter has been added by way of this amendment. Claim 9 has been amended herein to recite that the antibody-terminated PDMS is capable of binding to the ligand. Specific support for this amendment is found in the specification, at for example, Example 9, paragraphs 179-182 and illustrated schematically in Figure 12 in which various antibodies are conjugated to the PDMS and are then shown to specifically capture ligand. No new matter has been added by way of this amendment. Thus the rejection is overcome and should be withdrawn.

Claim 7 is further rejected as being incomplete for omitting essential elements. Specifically, the claim is rejected because the Office states that the omitted elements include phospospecific antibodies that are used to detect phosphorylated proteins. The claim has herein been amended to depend from claim 6 and to recite that the peptide moiety is an antibody moiety. Specific support for this amendment is found in the specification at for example, [Para 181]. No new matter has been added by way of this amendment. Thus, this rejection is overcome and should be withdrawn.

Claim 8 is rejected because it recites an "antibody terminated" PDMS. While the applicants believe that the antibody termination of the PDMS is fully described in the

specification, the claim has been amended herein to recite that the peptide moiety is an antibody. The use of terminal antibodies as ligand receptors is described in the specification at, for example, [Para 181]-[Para 182] and further at Example 12, [Para 197]-[Para 202] and illustrated schematically in Figure 12. Thus, the rejection has been overcome and should be withdrawn.

Claims 13 and 14 recite the limitation "the array" for which the Office finds insufficient antecedent basis. However, as claim 1 has now been amended (see above) to recite in part (a) that the affinity substrate comprises an array, antecedent basis is provided for the limitation recited in claims 13 and 14. Support for this amendment is found in the specification at, for example, Para [23], [37], [74] and Example 9, [Para 179-181]. Thus the rejection has been overcome and should be withdrawn.

Claim 13 is further rejected for reciting the limitation that the receptor "independently has specificity for one ligand" and that the liquid crystal is capable of detecting the presence of "more than one ligand." As discussed above, in part 4, the receptors are specific for a specific epitope. In some cases, the specific epitopes may be on the same ligand and in other instances, the specific epitopes may be on different ligands. In the case of the receptors discussed in paragraph [181], the receptors are specific not just for specific epitopes on the same ligand but some (pY1068, pY1086, pY1148 and pY1173) only bind when the specific epitope is phosphorylated. Thus, each species of receptor is specific to its particular binding site (residue) on the ligand. Therefore, the rejection is traversed in part and overcome in part because the specification at, for example, paragraph 0181 clearly describes the binding site (residue) of the antibody on the same ligand. Further, as discussed above in part 4, the nomenclature of naming antibodies to specify their cognate binding site on the ligand was developed well before the invention was made. Thus, those of skill in the art would immediately recognize that the recognition site of the antibodies described would be the phosphorylated tyrosine at residues

1068, 1086, 1148 and 1173 respectively. Recognition of this state of the art is independently attested to by the nomenclature and description of provided in the product data sheets included in Appendix I and in various standard texts on immuno-chemistry. Therefore, the rejection is overcome and should be withdrawn.

Thus, the receptors discussed allow the liquid crystal to detect the presence of each specific cognate binding partner whether the binding partner is a different epitope on the same ligand or an a different ligand. Claim 13 has been amended herein and no longer recites the limitation cited by the Office. Further, as discussed above, the amendment that the "change in orientation of the liquid crystal . . ." finds specific support in the specification, at for example, [Para 189] where multiple antibodies are used to detect various ligands. No new matter has been added by way of this amendment. Thus, this aspect of the rejection is overcome and should be withdrawn.

Claim 13 is further rejected because it is unclear what relationship the "one ligand" and the more than one ligand" that are recited in claim 13 have with the "ligand" of claim 1. As amended herein, claim 1 now recites, in part, that ". . . the affinity substrate comprises an array of receptors wherein each receptor is capable of specifically binding to a ligand." Further, claim 13 has herein been amended to recite that "each receptor in the array has specificity for a ligand" and further that the "liquid crystal is capable of detecting the presence of the receptor-bound ligand." Thus, the relationship between the one ligand and the more than one ligand is made clear. Specific support for this amendment is found, for example, in the specification at for example paragraphs [181-193] and Figures 12-17. No new matter has been added by way of this amendment. Thus, the rejection is overcome and should be withdrawn.

Claim 13 is further rejected because it is unclear what is meant by the adjective "independently". As amended herein, claim 13 no longer recites the adjective "independently". Thus, the rejection is overcome and should be withdrawn.

Claim 18 is rejected as indefinite because the term "partially curved affinity substrate" suggests that the affinity substrate is inherently curved. As amended herein, the claim now recites that "a portion of the affinity substrate is curved." Specific support for this amendment is found in the specification at, for example, paragraphs [89] and [137] which describe the stamping procedure used when the stamp is mounted to a cylindrical scintillation vial. As the vial is cylindrical and as a cylinder is defined as "the surface traced by a straight line moving parallel to a fixed straight line and intersecting a fixed planar closed curve" (Merriam-Webster Online Dictionary). Thus, a portion of the surface area of the cylinder must reflect the curve. Further, the surface area of a cylinder is defined as a curve expressed by the equation $2\pi Rh$. Therefore, a stamp mounted to a cylindrical scintillation vial must have a priori, at least a portion of the affinity substrate curved. Thus, this rejection is overcome and should be withdrawn.

3. Claim rejections under 35 USC § 103

In the Action claims 1-5, 8-11, 13, 15-20 and 22-23 were rejected under 103(a) as being unpatentable over Bernard et al. in view of Abbott et al. Claims 6-7 were rejected under 103(a) as being unpatentable over Bernard et al., in view of Abbott et al. as applied to claim 1 and 5 and further in view of Houseman et al. Claim 14 was rejected under 103(a) as being unpatentable over Bernard et al in view of Abbott et al. as applied to claims 1 and 12 and further in view of Tang. Claim 21 was rejected under 103(a) as being unpatentable over Bernard et al. in view of Abbott et al as applied to claim 1 above and further in view of Tarlov et al. However, as pointed out below, the combination of Bernard et al. and Abbott et al. do not include all the elements of the present invention and further the combination of steps taught would not result in the

presently claimed invention. In addition, neither Houseman et al., Tang, nor Tarlov cure the defects of Abbott et al. and Bernard et al. As discussed below, the rejection is in error and should be withdrawn.

3.1 The Office has not made a *prima facie* case

The MPEP is clear "[T]o establish a prima facie case of obviousness, three basic criteria *must* be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference. Second there must be a reasonable expectation of success. Third, the prior art references must teach or suggest all the claim limitations. MPEP 2143. Without satisfying all three criteria, a *prima facie* case is not made and the rejection is improper.

3.1a There is no motivation to combine the references

In the instant case, none of the three requirements necessary to make a prima facie case are present. First, there is no motiviation to combine the references. One goal of the instant application is to provide a method of detecting a ligand that does not require the use of radioactivity or fluorescence staining or other post detection procedures. Bernard simply does not contemplate such other methods or allude to them. Further, Bernard is directed to means of facilitating "biological experiments at the solid/liquid interface" (see abstract). In addition, as taught by Bernard, "[T]he release of captured target molecules and their transfer to the printed surface is an intriguing phenomenon and *may seem counter-intuitive.*" (See, Bernard et al., page 866 last paragraph). Such counter-intuitive ideas specifically teach away from making the combination made by the Office. Further, Bernard et al pose the question "[T]o what purpose might the attributes of selectivity and directed release of αCP be applied best? Neurons are particularly difficult to attach and cultivate . . . . A significant feature of the αCP technique is the ease of producing patterned protein layers, which can be used to guide cell attachment and

outgrowth of cells" (See, Bernard et al. page 868, first and second full paragraphs). Thus, Bernard et al. specifically teach the use for the method disclosed therein is the field of cell biology and cell culture. These fields do not readily recommend themselves to identification of ligands as described in the Abbott reference cited by the Office. Thus, there is no motivation to combine Bernard et al. with Abbott et al.

Further, there is no motivation in Abbott et al. (the '285 patent) to combine the '285 patent with Bernard et al. The Office cites to column 17, lines 5-22 in the '285 patent for the proposition that the surface taught by Abbott is compatible with microcontact printing taught by Bernard et al. This is untrue. As described in the '285 patent, at col. 17, line 5 the substrate (i.e. the glass slide, see previous paragraph) that contacts the mesogenic compounds can be prepared by a variety of methods by which the mesogenic compounds are adhered to a substrate (e.g. glass slide). These methods include deposition by evaporation, photoetching, chemical etching and microcontact printing. As further stated in the '285 patent "the patterning is used to produce a substrate having a plurality of adjacent wells, wherein each of the wells is isolated from the other wells by a raised wall or partition and the wells do not fluidically communicate. Thus, an analyte, or other substance, placed in a particular well remains substantially confined to that well. In another preferred embodiment, the patterning allows the creation of channels through the device whereby an analyte can enter and/or exit the device" (Col. 17, lines 23-31). Thus, as explicitly described by the '285 patent the microcontact printing mentioned is practiced to prepare a substrate upon which or in which a mesogenic layer is formed and/or confined. This constitutes a preliminary step to prepare the substrate allowing the after-addition of the analyte. The '285 patent, in certain embodiments, then describes the deposition of organic layers (SAM) that are added to the substrate/analyte to anchor the mesogenic layer thereto. As well, a further SAM layer may be layered on top of the mesogenic layer (See, col. 20, lines8-16) with, finally, a

recognition moiety attached to functionalized spacer arms or SAM components. (Col. 26, lines 21-25). Microcontact printing is therefore not described by Abbott et al. in the context of transferring a ligand or target to a mesogenic detection surface but, in fact, only in the context of preparing a surface upon which a liquid crystal is then provided, before a detection step ever takes place. Thus, Abbott et al. do not teach the steps of transferring a ligand/target to a liquid crystal-prepared surface in the context of a detection step and, accordingly, the Office's reliance on this cited reference is unfounded. In fact, Abbott et al. make mention of microcontact printing only in the most general sense as it relates to preparing a single substrate surface upon which a liquid crystal or liquid crystal/SAM layer is then formed prior to any detection step.

3.1b There is no reasonable expectation of success

As to reasonable expectation of success, the statements of Bernard discussed above do not lead one of skill in the art to contemplate a reasonable expectation of success. Rather, one of skill in the art, in trying to devise a method of identifying ligands would not look toward Bernard, which is "counter-intuitive" and which is best used for propagating hard to culture cells such as neurons.

The reference to microcontact printing by Abbott et al. refers solely to the preparation of the substrate upon which the liquid crystal is placed/confined. The '285 patent simply does not use or contemplate the use of microcontact printing in the detection context to, specifically, contact a detection substrate with an affinity substrate as is presently claimed. According to the '285 patent, patterning of a "base" surface is simply a preliminary step necessary, in certain embodiments, followed by the deposition of a mesogenic layer and further overlay with a SAM layer. Thus, there is no motivation to combine Bernard et al. with Abbott et al. because ***the combination would not yield the claimed method and device of the present invention***. The

combined references provide no expectation that transfer of ligands/targets to the surface of liquid crystal detection surfaces would be expected to be successful. Thus, this part of the rejection is overcome and should be withdrawn.

3.1c The combination does not include all of the elements of the present invention

Even when taken together, *the combination of Bernard and Abbott do not teach all the elements of claim 1*, i.e., an array of receptors that detects one or more ligands via the change in orientation of a liquid crystal in contact with the detection surface. Specifically, in the instant application claim 1 recites a method where a) a sample is contacted with an affinity substrate, the affinity substrate having an array of receptors; wherein each receptor is capable of specifically binding to a ligand wherein in the presence of the ligand, the receptor specifically binds to the ligand and b) contacting the affinity substrate with a detection surface, wherein at least a portion of the ligand which is bound to the receptor is transferred to the detection surface; and (c) detecting the presence of the ligand on the detection surface using a detection substrate having a liquid crystal, wherein the presence of the ligand is detected by a change in the orientation of the liquid crystal. That is, the invention comprises independent and distinct affinity substrates and detection substrates (see, for example, Para [64]-[66]). As noted above, the '285 patent simply does not use or contemplate the use of an affinity substrate for use in microcontact printing a detection substrate which then results in a detectable orientation change of a liquid crystal. *The combined references do not teach nor do they suggest the transfer of an analyte to a liquid crystal containing surface* and therefore the combined teachings lack elements of the claimed invention, namely, the steps of using an affinity substrate to stamp or transfer to a liquid crystal containing detection surface. While the '285 patent generally mentions affinity stamping, the context of that disclosure is in preparing a surface upon which a mesogenic layer will be

provided /confined not in the sense of transferring ligand/target to an already formed liquid crystal detection surface.

A significant result of the design of the invention, as claimed (see claim 2) is that both the affinity substrate and the detection substrate can be washed and reused, either to identify the same ligands (in the case of the affinity substrate) or a new detection involving different ligands (in the case of the detection surface). See for example, paragraphs 19 and 30. In contrast, the '285 patent does not teach the use of an independent affinity substrate and detection surface. As taught by the '285 patent "the present invention provides a device comprising: a first substrate having a surface, said surfaced comprising a recognition moiety; a mesogenic layer oriented on said surface; and an interface between said mesogenic layer and a member selected from the group consisting of gases, liquids, solids and combinations thereof. (See, '285 patent at col. 13, lines 30-35 and col. 14, lines 10-47). Thus, as taught by the '285 patent, the mesogenic layer is an integral component of the surface containing the recognition moiety. In fact, the '285 patent specifically teaches that the invention provides a method comprising: "(a) contacting with said analyte a recognition moiety for said analyte, wherein said contacting causes at least a portion of a plurality of mesogens proximate to said recognition moiety to detectably switch from a first orientation to a second orientation upon contacting said analyte with said recognition moiety; and (b) detecting said second configuration of said at least a portion of said plurality of mesogens, whereby said analyte is detected." (See, '285 patent at, col. 14, lines 36-47). Thus, not only does the '285 patent fail to teach the use of individual affinity substrates and detection surfaces, but as taught, the '285 patent fails to describe any such combination of surfaces or devices that may be reusable in the context of specific recognition and detection.

Further, the teaching of Bernard does not cure these defects. Bernard does not mention or even contemplate a detection surface that is reusable or that is composed of liquid crystals.

Thus, the detection surface of Bernard et al. merely serves as a platform for capturing a target molecule, the presence of that target molecule is then detected by further processing steps of visualizing the streptavidin-bound, biotin-labeled alkaline phosphatase (target molecule) by enzymatic methods (See, Bernard et al., page 867). Thus, as taught by Bernard et al., the affinity stamp is only reusable for making multiple "contact prints" with the same stamp preparation (i.e. it is not washable and reusable with multiple potential target extracts, the substrate is not reusable at all and finally, the process taught by Bernard et al., is limited to the use of the streptavidin-biotin attraction and methods for enzymatic identification of the target (which is required to be either streptavidin conjugated or biotin conjugated).

Therefore, taken together, the combination of the '285 patent and Bernard et al. fails to teach the use of separate affinity substrates and detection surfaces, or the use of the invention using an array of receptors. Thus, the rejection over the '285 patent and Bernard is improper and should be withdrawn.

Further, as noted in the instant application when reviewing the prior art "such assay devices use the same surface for both the capture and detection of the target. Because a single surface is used for both capture and detection, the surface cannot be optimized to perform both functions." [Para 15] As further noted, "proteins adsorbed to the surface of a PDMS stamp will be transferred to a second surface when the second surface possesses a surface energy that is higher than that of PDMS." [Para 16] In meeting this need, the inventors note that by using high energy surfaces in air, the invention inherently possess two functional properties i.e. 1) the surfaces must capture the analyte from the affinity stamp; and 2) the surfaces, when supporting the captured analyte, must give rise to a set of orientations of the liquid crystal that are distinguishable from the orientations of a the liquid crystal on the surface in the absence of the captured analyte. The ability to use a second surface for detection is predicated on the ability of

the second surface to capture the target molecule. To this end the inventors note that by converting the affinity substrate and the detection substrate to high-energy surfaces, transfer of the ligand is enhanced. One method for facilitating such transfer is by pretreatment of either or the affinity substrate or detection substrate with an acid (see, [Para 64]). As noted in the application, "a hydrophilic SAM can be used to increase the transfer of protein from the stamp to the substrate . . . the increased transfer of protein to hydrophilic surfaces is believed to be the result of the high surface energy of hydrophilic surfaces exposed to air." [Para 93]. Thus, by omission of the optimization of functionality by physically separating the affinity and detection surfaces, both the '285 patent and Bernard et al. neither identify the advantages of the present invention nor allow for individual optimization of either the affinity substrate or the detection surface as is taught and presently claimed (see, e.g., claim 2). The additional references cited by the Office fail to cure the deficiencies of Bernard et al. and Abbott et al. Therefore, the combination of the '285 patent and Bernard et al. cannot make the present invention obvious.

Because the Office has failed to make a prima facie case of Obviousness, the rejection over Bernard et al. in view of Abbott is overcome and should be withdrawn. Applicant's respectfully request same.

3.2 Amendments to further prosecution

As discussed above, the combination of Abbott et al. with Bernard et al. fails to teach or suggest the present invention. However, Applicant notes that, even given the Office's mischaracterization of the art, the Examiner acknowledges in the previous Office action, dated 7/12/2006 at page 12, 3rd paragraph, that the combination made by the Office provides all of the elements of the invention of claim 1 "since the claim does not require *different* types of receptors and *different* types of ligands." (emphasis in original) and that, following the amendment of the claims as amended in the response to the Office action of 11/21/2005 that "[T]he amended

claims do not require different types of receptors, only a plurality of receptors" (See, Id at page 18, last sentence). Thus, mindful of the Examiner's concerns and comments, claim 1 is herein amended to recite, in part:

1. A method for detecting [[a]] at least one ligand comprising

(a) . . . contacting a sample having or suspected of having a ligand with an affinity substrate, wherein the affinity substrate comprises [[a]] an ~~plurality~~ array of receptors;
wherein each receptor is capable of specifically binding to [[the]] a ligand and
further wherein in the presence of the ligand, the receptor specifically binds to the ligand and
further wherein in the presence of the ligand, the receptor specifically binds to the ligand; . . .

Specific support for these amendments is found in the specification at, for example, at paragraphs 181 and 182 in which different antibodies having different specificities are arrayed on the substrate. Specifically, [Para 181] describes an array including pan-reactive Ab 111.6 (Lab Vsion) phosphor specific Ab anti-pY1068 (Biosource), Ab anti-pY1086 (Biosource), Ab anti-pY1148 (Biosource) and Ab anti-pY1173 (Upstate). These antibodies all have different specificities for a ligand (see above and product analysis sheets for each antibody included herein for the Examiners Reference as Appendix I). In the instant example, the antibodies are specific to different epitopes of the same ligand. However, as illustrated by the different affinities of the antibodies and specificity to phosphorylated residues versus the lack of specificity to the same residue that is not phosphorylated; the experiments discussed in the present application show that the claimed method is sensitive enough to identify different epitopes of the same ligand or different ligands altogether. Thus, the amendment to claim 1 reciting "a array of receptors wherein each receptor is capable of specifically binding to a ligand" is explicitly supported by the specification. This amendment addresses the Office's concern that the combination of Abbott et al. and Bernard et al. could possibly describe all of the elements the originally claimed invention. However, since Bernard et al. only described the use of a single receptor and ligand

(avidin/biotin) on a modified target and since Abbott et al. only describes the use of a monolithic detection method and because the present invention describes and claims the use of an array of receptors capable of detecting multiple ligands the Offices concerns are unfounded. Therefore, the rejection is overcome and should be with drawn.

CONCLUSIONS

It is respectfully submitted that claims 1-11 and 13-23 are in condition for allowance and notice to that effect is earnestly solicited. The Examiner is urged to telephone the undersigned in the event a telephone discussion would be helpful in advancing the prosecution of the present application. The Office is authorized to charge the RCE processing fee, extension fees or any other surcharges or underpayment, as deemed necessary and appropriate, to the Deposit Account 07-1509 of Godfrey & Kahn, S.C.

Respectfully submitted,

GODFREY & KAHN, S.C.

Dated: January 12, 2007

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